REVIEW ARTICLE

Sports Med 2012; 42 (3): 185-208
0112-1642/12/0003-0185/$49.95/0

Circadian Disruption and Remedial Interventions

Effects and Interventions for Jet Lag for Athletic Peak Performance

Sarah Forbes-Robertson,[1] *Edward Dudley*,[2] *Pankaj Vadgama*,[3] *Christian Cook*,[4,5,6] *Scott Drawer*[5] and *Liam Kilduff*[1]

1 Sport and Exercise Science Portfolio, School of Engineering, Swansea University, Swansea, UK
2 Biochemistry Department, School of Medicine, Swansea University, Swansea, UK
3 Centre for Materials Research, School of Engineering and Materials Science, Queen Mary, University of London, London, UK
4 Hamlyn Centre, Institute of Global Health Innovation, Imperial College, London, UK
5 UK Sport, London, UK
6 Sport, Health and Exercise Science, Bath University, Bath, UK

Contents

Abstract

Jet lag has potentially serious deleterious effects on performance in athletes following transmeridian travel, where time zones are crossed eastwards or westwards; as such, travel causes specific effects related to desynchronization of the athlete's internal body clock or circadian clock. Athletes are particularly sensitive to the effects of jet lag, as many intrinsic aspects of sporting performance show a circadian rhythm, and optimum competitive results require all aspects of the athlete's mind and body to be working in tandem at their peak efficiency. International competition often requires transmeridian travel, and competition timings cannot be adjusted to suit individual athletes. It is therefore in the interest of the individual athlete and team to understand the effects of jet lag and the potential adaptation strategies that can be adopted. In this review, we describe the underlying genetic and physiological mechanisms controlling the circadian clock and its inherent ability to adapt to external conditions on a daily basis. We then examine the fundamentals of the various adaptation stimuli, such as light, chronobiotics (e.g. melatonin), exercise, and diet and meal timing, with particular emphasis on their suitability as strategies for competing athletes on the international circuit. These stimuli can be artificially manipulated to produce phase shifts in the circadian rhythm to promote adaptation in the optimum direction, but care must be taken to apply them at the correct time and dose, as the effects produced on the circadian rhythm follow a phase-response curve, with pronounced shifts in direction at different times. Light is the strongest realigning stimulus and careful timing of light exposure and avoidance can promote adjustment. Chronobiotics such as melatonin can also be used to realign the circadian clock but, as well as timing and dosage issues, there are also concerns as to its legal status in different countries and with the World Anti-Doping Agency. Experimental data concerning the effects of food intake and exercise timing on jet lag is limited to date in humans, and more research is required before firm guidelines can be stated. All these stimuli can also be used in pre-flight adaptation strategies to promote adjustment in the required direction, and implementation of these is described. In addition, the effects of individual variability at the behavioural and genetic levels are also discussed, along with the current limitations in assessment of these factors, and we then put forward three case studies, as examples of practical applications of these strategies, focusing on adaptations to travel involving competition in the Rugby Sevens World Cup and the 2016 Summer Olympics in Rio de Janeiro, Brazil. Finally, we provide a list of practice points for optimal adaptation of athletes to jet lag.

Although jet lag is generally accepted as a trivial consequence of aeroplane travel, it is classified as a 'circadian rhythm sleep disorder' by the *Diagnostic and Statistical Manual of Mental Disorders*,[1] the main psychiatric diagnostic textbook. The WHO also classifies it as a "disorder of the sleep-wake schedule".[2] Since so many physiological systems are controlled by the circadian clock, the effects of jet lag on the performance of elite athletes must be considerable.

1. What is Jet Lag?

Jet lag results from rapid transmeridian travel where time zones are crossed, such as east-to-west or west-to-east aeroplane travel. The severity increases with the increasing number of time zones crossed – travelling over three time zones almost invariably leads to jet lag.[3] No jet lag is experienced following north-to-south or south-to-north travel, regardless of the flight length, because transmeridian travel has a specific effect on the body clock – the internal clock ends up out of synchrony with external conditions. Jet lag symptoms occur while the clock tries to adapt.[4,5]

Normally, internal physiological rhythms are synchronized by the body clock to the external light-dark conditions. Humans are diurnal, primarily active during the day and asleep at night, and their circadian system therefore regulates physiology, such that waking occurs around sunrise and sleep onset is preceded by dim or no light, stimulating melatonin production.[6,7] This regulation is disrupted by transmeridian travel, and normal activities, such as sleeping, waking and eating, can therefore occur in abnormal external light-dark conditions.

Circadian rhythms are internally generated rhythms that persist in the absence of external cues, such as light or darkness. In this way, organisms can time their behaviour without referring to external conditions, allowing them to anticipate external conditions rather than merely reacting. This can be demonstrated by maintaining individuals in constant conditions: cyclic behaviour persists even with no, or only very weak, external time cues.[8-10] Disruptions therefore ensue following a rapid transmeridian travel, when external conditions conflict with the internal pacemaker.

Since the primary function of circadian rhythms is to allow adaptation to the external environment, the body clock is capable of adjusting to new conditions, but has evolved to adapt slowly to changes in day-length over several days and weeks, such as seasonal changes, rather than the abrupt changes caused by aeroplane travel. The fastest rate of adaptation is approximately half a day per hour of the time difference westwards, or 1 day per hour of the time difference eastwards.[3,11,12] However, the faster adaptation westwards is predicated upon the fact that the average human free-running period is about 24.2 hours,[8-10] and that individuals will therefore find it easier to adjust to a longer day than a shorter one. In actuality, substantial individual variation has been found to occur,[13-18] as discussed in section 3.2.

1.1 Effects of Jet Lag in Athletes

Athletes are particularly sensitive to disruption by jet lag as they are often required to travel long distances, such as for the Olympic Games, Commonwealth Games and other international competitions,[19] and then to perform at their best upon arrival. As coaches and athletes become increasingly aware of the effects of jet lag on performance, attempts have been made to minimize effects, such as early travel schedules, to allow adjustment to local time before competition; however, this is often not feasible.

Although the symptoms of jet lag vary between individuals, the main complaints are poor sleep, tiredness during the day, appetite loss and poor performance.[4,12,20-22] Transmeridian travel in either direction leads to a lack of sleep, mainly due to the inability to initiate sleep at a socially-required time and to maintain sleep for sufficient time, but also as a result of broken sleep often due to disrupted cycles, such as urinary frequency.[22] Eastwards travel causes problems falling asleep at bedtime, since the new ‘night’ occurs during the subjective daytime on the home-time schedule, whereas westward travel causes problems with early waking (figure 1). Daytime fatigue and poor alertness occur partly because of this sleep deprivation,[23] which can cause disturbances in hormonal secretion patterns in its own right,[24,25] but also because the body clock remains tuned to its night-time physiology during the new ‘daytime’, resulting in low core temperature and metabolism, and high levels of melatonin secretion.

There will also be specific effects of jet lag on athletic performance, as many aspects of exercise performance may show a circadian rhythm across the day. Improved performance has been reported to occur in the late afternoon (~16:00–20:00 home-adjusted time), with amplitudes of 2–11% of the daily mean.[26] Optimal performance in such areas as neuromuscular function, maximal oxygen uptake ($\dot{V}O_{2max}$) and grip strength also occur at this time and appear to parallel the peak in core temperature.[27] Other examples include peak force of leg and back muscles,[28-32] arm muscles,[33,34] maximal anaerobic power output[35] and performance in broad and vertical jumps.[36] Performance in simulated contests or time trials has also been shown to have a similar daily rhythm with similar peak times, including running,[37] swimming,[38-40] cycling[41-47] and skilled tasks related to football,[48] as well as other surrogate performance markers (see Drust et al.[49] and Hayes et al.[50] for reviews).

All these physiological measures are susceptible to disruption by jet lag, as the internal timings for peak performance will be out of synchronization

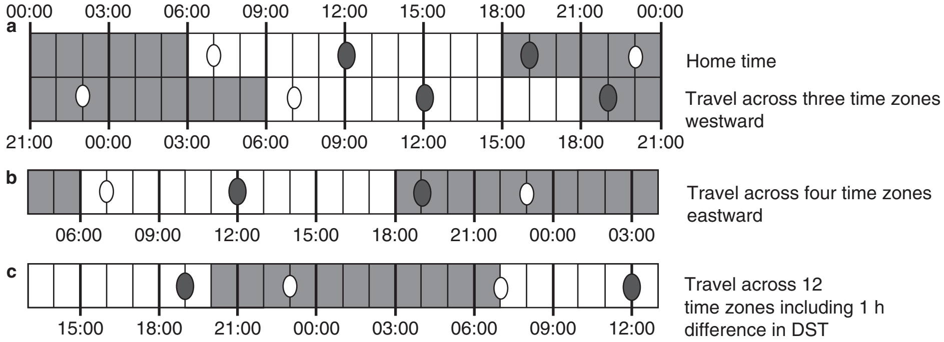

Fig. 1. Transmeridian travel time zone effects are shown graphically in the following panels. The upper panel shows home time, and the lower panels show time at the destinations, aligned with home time to show times of potential exposure to daylight following travel; grey boxes indicate night, white boxes indicate daylight; white ellipses show normal sleep and wake onset times, taken as 23:00 and 07:00 on home time, respectively, and black ellipses show meal times [midday meal at 12:00 and evening meal at 19:00 home time; actual daylight times are taken from average sunrise and sunset times in March around the Vernal Equinox with the UK as home time]. (**a**) Travel across three time zones westwards (–3 h time difference): normal home wake time now occurs in the middle of the night; normal sleep time is 3 h before destination sleep time leading to feelings of tiredness many hours before destination sleep time. Attempts to adjust directly to local timings upon arrival would lead to a sleep time at 02:00 home time. If athletes were able to stay awake until this local sleep time, they would probably still wake at their normal home wake time, after only 5 h of sleep. Attempts to adjust directly to local meal times result in lunch at 15:00 home time, and the evening meal at 22:00 home time, shortly before the normal home sleep-onset time. (**b**) Travel across four time zones eastwards (+4 h time difference). Normal home wake time now occurs at approximately 12:00, and normal sleep time at 03:00. Attempts to adjust directly to local timings on arrival would result in a sleep time at 19:00 home-time hours before they are likely to feel tired, and wake time at 03:00 after only 4 h of sleep after onset of normal home sleep time. The normal home 12:00 meal time now falls at 16:00 and the home evening meal at 23:00 after the onset of expected sleep time if adjusted to local time. Attempts to adjust directly to local meal times on arrival would place the 12:00 meal at 08:00 home time, which is shortly after the home wake time; and the evening meal at 15:00 home time. Both of these are times when the athlete is unlikely to feel especially hungry. (**c**) Travel across 12 time zones with 1 h of additional daylight savings time change, as seasons are opposite at the Antipodes (+13 h time difference). Normal wake time (07:00) now coincides with the onset of night at the destination, and home sleep time occurs at 11:00, during full sunlight at the destination. The normal home midday meal occurs at 01:00, in the middle of the night, and the evening meal falls at 08:00 in the morning. Attempts to adjust directly to local time on arrival would result in a midday meal at 23:00, approximately 4 h after the expected home evening meal timing and the evening meal would occur at 06:00 home time, potentially leading to a requirement for the heaviest meal to be consumed before the athlete's normal wake time. **DST** = daylight savings time.

with external conditions following travel, and these effects may last for a considerable time. Consider an athlete who is synchronized to their local environment and has a peak in sport performance at 21:00; if the difference between the maximum and minimum of peak performance is postulated as 1%, then an elite male runner would be 2 seconds slower in a 1500 m race and 75 seconds slower in a marathon run following air travel across 12 time zones.[51] Although some studies have shown no effect of jet lag on performance, despite changes in physiological markers,[52,53] other studies have shown that performance and physiological functions may be depressed for several days as they remain out of phase with local conditions.[54,55] For example, in 40 m sprint tests in elite women hockey players travelling from Australia to Europe, recovery took 8 days, for travel crossing 6 time zones. Statistical analyses have also shown negative effects even of short flights on performance, by analysing results of American football, netball and basketball teams flying coast to coast before a match.[56-59]

In many sports, performance also depends on factors outside the purely physical realm, and jet lag has been shown to negatively affect cognitive performance, possibly through sleep-loss effects[60-62] and motivational effects.[63] There are also possible long-term consequences of frequent jet lag, including cognitive defects, depression, increased risk of mood disorders, increased cancer risk, infertility, cardiovascular disease and brain atrophy.[64-79]

Although symptom severity varies between individuals, many athletes may simply fail to recognize how they are affected by jet lag, especially in tasks requiring concentration and complex coordination. For example, they may have difficulty sleeping at the appropriate time following transmeridian air travel, but ascribe this to stress or effects of the flight, rather than recognizing it as jet lag.[80] Further education is therefore required to allow athletes to identify the symptoms of jet lag to properly address them.

1.2 The Circadian Clock

Regulation of the circadian clock lies in a complex series of interlocking feedback loops.[6,7,81] The key genes involved in the circadian system are called ‘clock’ genes.[82-89] The positive feedback loop ‘clock’ genes, *BMAL1* and *CLOCK* turnon gene expression of the *Period* (*Per*) and *Cryptochrome* (*Cry*) ‘clock’ genes, which in turn act to inhibit *BMAL1*/*CLOCK* expression and, hence, their own expression in a negative feedback loop. Only when expression of the inhibitor genes falls below a threshold level can the positive ‘clock’ genes turn expression back on (figure 2a). This coordinated rise and fall of ‘clock’ gene expression in a sine-wave pattern[91] acts as an internal timekeeper, allowing precisely-timed control of other downstream processes, resulting in specific physiological effects at specific times of the day-night cycle, such as the 24-hour cycle of core temperature[92,93] (figure 2b).

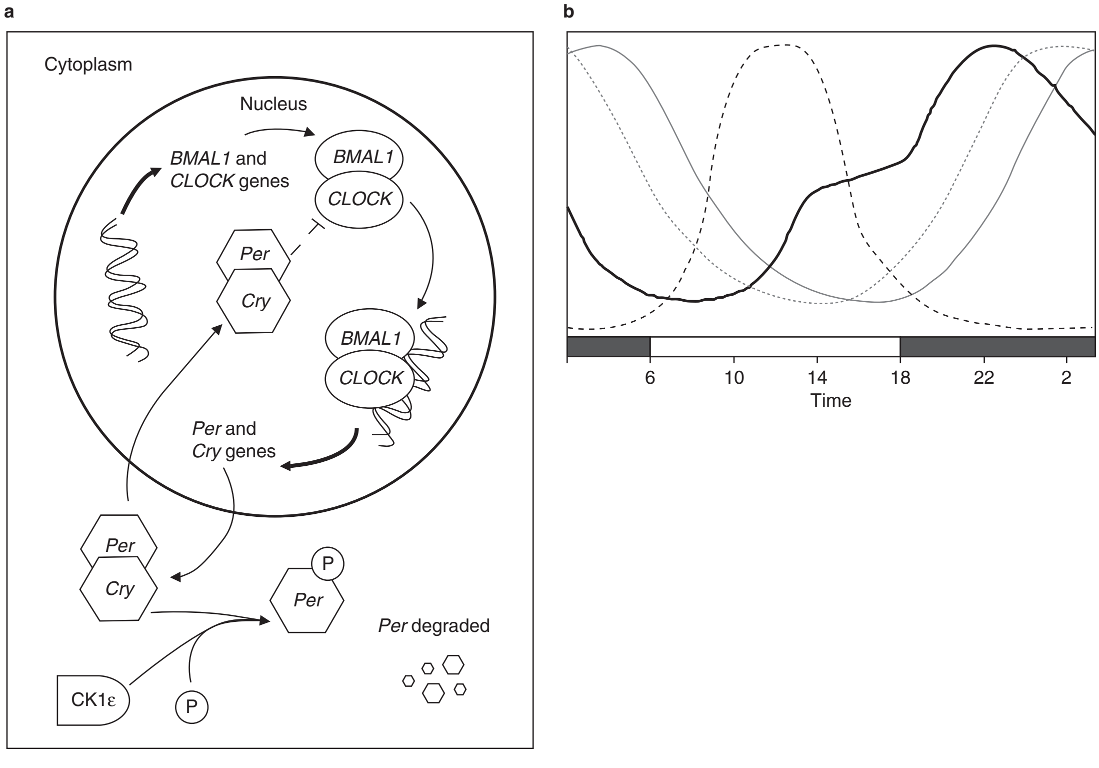

Fig. 2. Circadian clock mechanism. (**a**) When they are expressed together in the 24 h cycle, the CLOCK and BMAL1 proteins bind together. This active BMAL1-CLOCK heterodimer acts as a transcription factor to turnon expression of the *Period* (*Per*) and *Cryptochrome* (*Cry*) genes. These are then translated into protein form in the cytoplasm, where they bind together to form a complex that is transported back to the nucleus, and acts to inhibit *BMAL1* and *CLOCK* expression in a negative feedback loop. This in turn reduces the activation of expression of the *Per* and *Cry* genes themselves, and it is only when their expression levels drop below a certain threshold that sufficient CLOCK and BMAL1 protein can be produced to turn their expression back on. Other factors also regulate the circadian clock at the protein level, such as casein kinase 1 epsilon (CK1ε) that phosphorylates *Per2* and induces its degradation [adapted from Biocarta,[90] with permission] (**b**) Circadian gene expression typically follows a sine-wave pattern, with one peak and one trough in expression across the 24 h period. Genes shown are transcript levels for *Per2* (solid black line), *Rev-Erbα* (large black dashed line), and *Cry1* (small grey dashed line). Downstream physiological measures, such as core temperature, also follow a similar circadian pattern (solid grey line).[91,92]

As this system regulates so many key physiological processes, it is itself tightly regulated at many levels. For example, multiple human *Per* and *Cry* genes (*Per1*, *Per2* and *Per3; Cry1* and *Cry2*)[85,94] have been identified,[95] all of which may play overlapping or independent role.[96] Other genes, such as *NPAS2*, *Rev-Erbα* and *ROREα*, add extra levels of control,[97-99] and regulation of protein turnover is also central to regulating timing[95,100-102] (figure 2a). Given the complexity of this system and the multiplicity of downstream physiological processes, perturbations caused by jet lag can cause complex effects, and hastening realignment is not a simple process.

1.3 Readjusting the Clock: Zeitgebers

The primary function of circadian rhythms is to allow organisms to adapt to environmental variations; this is achieved by having an internal rhythm at slight variance to the external 24-hour period and resynchronizing the internal rhythm to external cues every day. Under experimental conditions of constant light or dark, the average human free-running period is about 24.2 hours,[8-10] approximately the length of 1 day-night cycle on earth, but some people show a slightly shorter period and others a slightly longer one.[103]

Under normal conditions, external factors serve daily to resynchronize the circadian clock to a 24-hour cycle, these are classically called ‘zeitgebers’ (‘time-givers’ in German) and the most important one in vertebrates is the external light-dark cycle. Other much weaker zeitgebers include food, exercise, sleep and pharmacological treatments that mimic the endogenous hormones involved in the clock.

The major zeitgeber, sunlight, resets the circadian rhythm primarily via circadian-specific receptors in the retina.[104-109] These then project directly to a brain region in the hypothalamus, called the suprachiasmatic nuclei (SCN),[6] which acts as a master clock. If the SCN is surgically ablated in rodents, they lose all circadian rhythm and are active at random times.[110] Until 1996, it was therefore believed that the SCN was the only clock in the circadian mechanism. However, it has now been found that individual organs,[111-122] and even single cells,[6,123] maintain their own individual clocks. Synchronization of all these peripheral rhythms is required for optimal physiological function, and differences in the rates of recovery of these peripheral clocks following transmeridian travel are thought to account for many of the symptoms of jet lag.[124]

Experiments to examine organ desynchrony in humans are difficult to perform; however, in rodents, *Per* gene rhythms in the SCN readjust rapidly following simulated jet lag, in <24 hours, but peripheral organs, such as the liver, lung and muscle, can take nearly six times as long to adjust[125,126] depending on the animal model used,[127] and they appear to be entrained by cues other than light.[128] In humans, the sleep rhythm causes the greatest apparent symptomatic problems but tends to adjust more quickly to the new environment than the temperature rhythm, gastrointestinal and most endocrine rhythms.[4,5] Athletic performance is likely to be suboptimal until the whole spectrum of biological rhythms adjusts to the new time.

1.4 Timing of Adjustment: Phase-Response Curves

The key to understanding how the internal circadian clock responds to external conditions and how athletes can use these to minimize jet lag is the phase-response curve (PRC). The circadian clock is altered by zeitgebers in different ways at different times: it is affected most by unexpected conditions, such as light during the night[129] or the presence during the day of hormones usually associated with sleep onset, such as melatonin.[130]

The PRC shows the direction and magnitude of phase shift induced in the circadian rhythm at different times (figure 3). There is a transition point where the effect of the zeitgeber switches from delay to advance. For example, while exposure to light in the late afternoon and early evening on home time produces a delay in the clock and shifts ‘internal’ wake-sleep and meal times to later in the day, light stimuli in the second half of the night or early morning results in an advance in the clock that shifts ‘internal’ times to an earlier hour.[129,131] This crossover point also correlates with the core

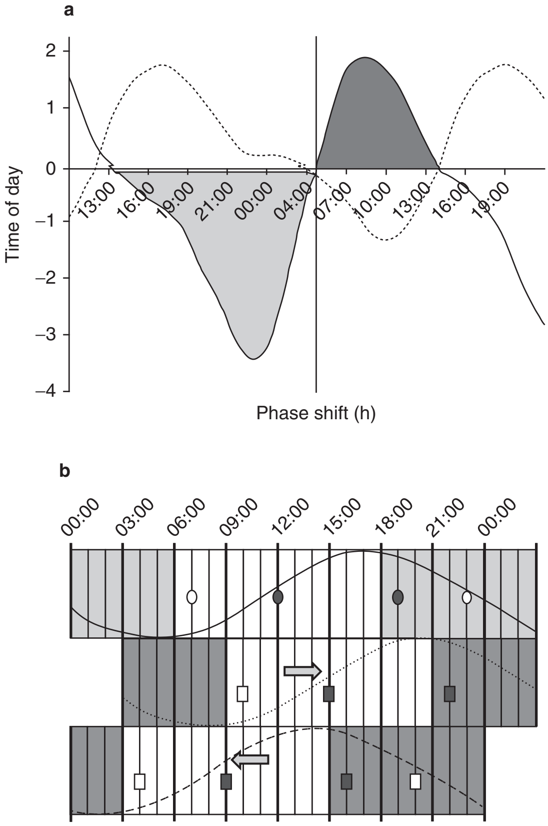

Fig. 3. A phase-response curve (PRC) shows the effect of a particular stimulus on the circadian clock throughout the entire circadian cycle. (**a**) The phase-response curve for light (solid line) and for 3 mg of melatonin (small dashed line). The light data shows the effect of a single light stimulus in young adults using plasma melatonin as a marker for circadian rhythm plotted relative to the centre of the light stimulus. By convention, delays in the circadian rhythm (shifts to a later hour) are shown as negative numbers, and advances (shifts to an earlier hour) are shown as positive values. Datapoints are double-plotted to generate two cycles to better visualize the response pattern.[131,132] (**b**) The effects of light exposure at different times in the PRC are shown here. The top section shows home external time and light/dark conditions. Light exposure in the late evening and first half of the home night [see the light grey area on the phase-response curve in (**a**)] causes adjustment in the internal circadian clock by a phase delay, shown in the middle section, such as that required for adjustment following east-to-west travel; whereas, light exposure in the second half of the night and early morning [dark grey area on the phase-response curve in (**a**)] causes adjustment by a phase advance in the clock, as required following west-to-east travel, shown in the bottom section. Light grey panels indicate night, white panels indicate daylight; white ellipses show normal sleep and wake onset times, taken as 23:00 h and 07:00 h on home time, respectively, and black ellipses show meal times (midday meal at 12:00 h and evening meal at 19:00 h, home time), curved lines show core body temperature rhythm with dashed lines showing body temperature after phase advance or delay. Dark grey panels indicate 'internal night' as expected following the phase shift, and black and white small boxes indicate new 'internal' wake, sleep and meal times.

body temperature low point. Care must be taken when timing interventions around the crossover point to ensure that the required effect is achieved, especially since this point can show individual timing variation.

The PRC also shows when the clock is less responsive to zeitgebers, primarily at the times when they would normally be expected to occur. For example, during the day, from approximately 2 hours after usual wake-up time until 2 hours before usual bedtime, light has relatively little effect on the circadian rhythm.[129,131-133] The response is also dose-dependent, with strong light having more of an effect than weak light.[134,135] Higher doses of chronobiotic drugs, such as melatonin, tend to have greater effects[136] but correct dose-timing appears to be more critical at supraphysiological levels.[130,137,138]

These PRCs can be used to plan the optimum times to apply stimuli to best effect jet lag recovery, and to avoid applying stimuli that would cause the clock to become further desynchronized; however, care must be taken, as variation exists between individuals in the precise PRC timings,[139,140] as discussed in section 3.2.

2. Practical Applications: How to Adapt Best

2.1 To Adapt or Not To Adapt? Short versus Long Trips

Whether to attempt adaptation to the local time zone depends on the trip duration. For short trips (1–2 days), attempts to adapt are not recommended,[141] as there are currently no instantaneously acting jet lag cures. The time frame is too short to achieve full adaptation by conventional methods, and any attempt may make the situation worse as the athlete will only partly adapt and will experience jet lag upon return, as they will be partly desynchronized with home conditions. Instead, it is recommended to try to stay on the home time zone, and to schedule important events at times of maximum alertness and performance on home timing (see section 1.1). However, in athletic competition, it is rarely possible to adjust event times to suit individual athletes.

Short-term methods to maintain alertness can be used, such as short naps[142,143] and stimulants such as caffeine.[144] Caffeine has been shown, specifically, to counter the effects of sleep deprivation on performance in a rugby passing skill test even at low concentrations;[145] however, the two jet-lag-specific trials have shown that the positive adaptation and stimulant effects of caffeine may be outweighed by negative effects on night-time sleep,[146,147] and question marks remain concerning the use of caffeine in sports, as a result of its general ergogenic effect.[148] Recently, the antinarcolepsy drug modafinil has been licensed for use in shift-work sleep disorder in the US,[149] and it has been suggested to be useful for maintaining daytime alertness in jet lag.[141] However, there is no published data on its use in jet lag, and modafinil is a substance banned in competition on the World Anti-Doping Agency's (WADA) 2010 Prohibited List.[150]

Short-acting sleeping pills, such as zolpidem, are often recommended for jet lag in businessmen to induce sleep pharmacologically during the new destination night-time,[144] rather than any direct circadian effect. While these drugs are not specifically proscribed by WADA, the timing of administration must be tightly controlled to prevent performance inhibition and adverse effects on sleep timing.[151] The British Olympic Association has advised against using sleeping pills when competing overseas, and emphasized that team physicians and support staff should be consulted regarding their use.[152]

For longer stays (>4–5 days), strategies can be designed either to support adaptation upon arrival or to promote adaptation to the new time zone before the trip even begins. These strategies depend on reinforcing the normal zeitgebers, such as light, food, sleep regimens and exercise, with stronger-than-normal cues, or cues at new times, to synchronize the circadian phase to the destination time zone. Theoretically, using a combination of all the available time cues at their optimal times should show the best result in terms of adaptation. Additive effects have been seen, such as with bright light and melatonin,[153,154] but in practice, the timings must be carefully calculated and the extent of interaction is unclear.[155,156]

2.2 Light

Light is one of the strongest natural cues for resetting the circadian rhythm and exposure to ambient light after transmeridian travel largely controls the direction and speed of adjustment. As described in section 1.4, the effect of light on the circadian clock follows a PRC (figure 3a) and timing, intensity and even wavelength all play a significant part, as well as the pattern of previous exposure (reviewed in Duffy and Czeisler[131]). It has also been suggested that two different light-entrainment mechanisms may operate in humans,[131] as phase shifts of 2–3 hours are usually elicited by exposure to light,[129] but some earlier studies produced large shifts of up to 12 hours.[132,133]

One of the simplest jet lag strategies is to promote and restrict exposure to natural sunlight at specific times. This strategy is simple, as no specialist equipment is required, but exposure must be carefully timed according to the PRC to avoid unwanted effects (figure 3b). Following westward travel, according to 'home' time rather than destination time, light exposure should be actively sought in the early evening and first half of the night to cause a phase delay but avoided in the second half of the night and early morning, as it will cause a phase advance.[129,157] The opposite is true following eastwards travel. Although exposure to sunlight can often be managed, it is much harder to completely avoid light exposure on the plane and on arrival and, for this reason, there is little substantial experimental evidence for the efficacy of this strategy.[158]

The calculations required to properly time light exposure and avoidance are not simple and will depend critically on the athlete's own personal PRC, which cannot be adequately measured at present using existing markers; however, numerous attempts have been made to simplify this process and create instructions for optimum timings. Various software algorithms and iPhone applications are available,[159,160] to allow individuals to plan the best adaptation strategy. Details of these strategies are discussed further in the case study examples in section 4.

Artificial light can also be used to enhance adaptation, with studies showing that multiple pulses of artificial light as short as 15 minutes can adjust the circadian clock.[161] This strategy shows considerable promise if the intensity and timing of the light exposure can be timed correctly; however, it also implies that even short bursts of light at the wrong time, such as in the night during airport transfers, can disrupt jet lag adaptation strategies. Additionally, evidence has also shown that bright interior electric light is only about one-third as effective as bright sunlight.[162]

The circadian system is most affected by blue light, since the photopigment in the retinal circadian light receptors, melanopsin, is maximally responsive to short wavelengths (460–480 nm).[104-106,109] Blue light also has the greatest effect on melatonin suppression[163] and can achieve the best circadian phase-shift response,[108,164] so much research and commercial interest has focused on the possibility of designing artificial lighting systems at exactly these wavelengths as jet lag aids. Preliminary evidence has shown that blue-enriched lights, such as those marketed for seasonal affective disorder, are more effective at maintaining alertness, quality and timing of sleep in office environments,[165] and in the Antarctic winter where natural daylight is limited.[166] Further research suggests that avoidance of this specific light wavelength, using glasses with filters, may circumvent the problems of light avoidance;[167] however, to date, little research has been published using such devices. There is some preliminary evidence showing that the optimal wavelength may also depend on the light intensity and that, under dim lighting conditions, green light may be more effective than blue.[141]

In summary, although research is still ongoing, it appears that the use of scheduled exposure to some form of artificial light will in future be the optimal method for entraining the circadian clock before and after aeroplane travel.

2.3 Melatonin

The pineal gland secretes the hormone melatonin during the hours of darkness, and it promotes sleep through vasodilatory effects causing a fall in core temperature.[168] Endogenous melatonin release begins around 2 hours before bedtime, just before dusk, provided that light conditions are dim, as production is inhibited by light.[169] Production is partly controlled by the SCN, with feedback through melatonin receptors on the SCN.[170] Desynchrony between the circadian clock and outside light-dark conditions leading to incorrectly timed melatonin release is primarily responsible for the sleep disruptions in jet lag. Melatonin is therefore of potential use as a treatment for jet lag and has received much attention as a chronobiotic;[171,172] the American Academy of Sleep Medicine recommends the timed use of melatonin supplements to promote adaptation.[173]

A Cochrane meta-analysis found a clear reduction of jet lag in eight of ten randomized trials of melatonin,[174,175] with a recommended dose of 2–5 mg for up to 4 days after travel. The response to melatonin is again dependent on a PRC (figure 3), and application must therefore be carefully timed and there may be individual timing variations. The PRC for melatonin is approximately 12 hours out of phase with the light PRC (figure 3b). Melatonin taken in the late afternoon or early evening on home time (not destination time) will advance the circadian clock, causing the body to act as though night-time has fallen early;[13,16,154,171,176] ideally, this would coincide with the onset of night at the destination, maximizing the sleep-inducing effects of melatonin. Melatonin taken in the early morning on home time should delay the body clock, fooling the circadian system that it is still night-time[177] but it has proven more difficult to convincingly show a phase-delay effect in humans[178] and only a limited number of direct studies have been performed, possibly requiring multiple doses.[16,130] Administration of too high a dose can also result in melatonin remaining in the bloodstream for too long, causing effects in the wrong portion of the PRC.[179]

Furthermore, although melatonin is classified as a chronobiotic and has been reported as safe,[174,175] it performs multiple biological functions and is also used as a radioprotective agent, and to treat hypertension, drug toxicity and cardiac hypertrophy.[180,181] Specifically, melatonin should also be administered with caution in athletes as many countries have restrictions on its purchase and use. For example, in the UK, melatonin is considered as a medication and can only be prescribed by a doctor for licensed uses. Currently only one formulation, Circadin®,[182] has been licensed and is only for use in patients over 55 years of age. Import of melatonin is also prohibited in the UK, Brazil, Germany, Austria, Belgium, Canada, France and South Africa, amongst others. In the US, Singapore and Thailand, melatonin is considered as a food additive and is freely available from health food shops, but its purity is not regulated and care should be taken that it does not also contain substances banned by WADA.

Given the reported efficacy of melatonin as a chronobiotic, there is great interest in developing new formulations,[183,184] such as ramelteon (Rozerem®) and agomelatine (Valdoxan®). However, only limited clinical trial data is available to date on these drugs, and it remains to be seen what stand WADA and the licensing agencies in various countries will take on them.

2.4 Exercise

Research in rodents first showed that physical activity could affect circadian rhythms[185-187] and, although initial studies appeared to show no effect in humans,[188] during the last decade it has been shown that 1–3 hours of exercise can induce significant circadian phase shifts, although the effects depend on duration, intensity and frequency.[189,190]

Early morning exercise has been associated with phase delays in the circadian clock,[191,192] and it has been suggested that early evening exercise can result in phase-advances;[193] however, the evidence is conflicting. In some studies, exercise during the biological night induced phase delays in melatonin secretion but not core temperature, while other studies showed the opposite effects (reviewed in Atkinson et al.[194]). Other studies have shown no effect of exercise on melatonin secretion in simulated jet lag, but an acceleration of adjustment of sleep-wake cycles.[195] Some evidence also exists that multiple exercise sessions per day have different effects than a single session[195] and that high levels of exercise are required to show any effect on circadian rhythms, such as 3 hours at 50–60% of $\dot{V}O_{2max}$.[189] These conflicting results could arise from differences in the time of day and intensity of exercise, lighting conditions, gender and age.[194] Care must also be taken when applying the results of studies performed with participants who are unused to physical training to those who are highly trained elite athletes, especially since many studies aimed to examine the effects of exercise on poor sleep in elderly patients.[191] Conflicting evidence also exists regarding the effect of fitness on speed of adaptation, with some studies reporting improved adaptation and decreased jet lag symptoms in individuals with greater fitness,[54] and others suggesting that fitness can exacerbate jet lag symptoms.[196]

In a recent review of physical activity and circadian rhythms, Atkinson and Davenne[197] concluded that further research is required to identify the optimal amounts and timing of exercise required to reduce the effects of shift work and jet lag.

However, since athletes are likely to be engaging in physical exercise both before and after travel, as part of their general training, appropriate scheduling could potentially allow them to take advantage of any synchronizing action of exercise and avoid detrimental effects. Generally, exercise appears to be required during the subjective night for optimum entrainment. Although the precise timings vary between studies, a recent meta-analysis gives the PRC for exercise as similar to that for light, albeit with a delay of around 2 hours for the crossover point, and with the phase-delay zone occupying the second half of that zone for light;[190,198] therefore, exercise could potentially be scheduled at the same time as light exposure in a jet lag strategy, but delayed by a couple of hours. Phase advances were predicted to occur when exercise was taken at home time in the late afternoon and early evening (16:00–19:00), but few studies have shown actual evidence of exercise-induced phase advances.[51,198]

2.5 Diet and Meal Timing

Feeding patterns follow a circadian pattern in many organisms, although this is often masked by environmental and sociocultural effects in humans. These circadian eating patterns are mirrored by both the gastrointestinal system and the liver, leading to rhythms in digestive secretions, gut motility, absorption of digested food and blood nutrient concentrations, all of which are critical for optimal sporting performance. Feedback loops exist between the hormones controlling the circadian clock and those directing appetite and satiety, such as leptin, orexin and ghrelin, and there is strong evidence for a specific food-entrainable circadian clock in many animals that is separate from the light-dark cycle.[199,200] It has been suggested that the liver and gut circadian clocks are predominantly entrained by feeding in mammals and only secondarily affected by light via the SCN.[128,201,202] However, few studies have been performed in humans, and although there is some support for the idea that eating meals at set times can enhance jet lag adaptation,[203] the situation is far from clear-cut as to the effect of such interventions.[204] Studies have shown that, even in animal models where food-entrainable clocks have been clearly identified, these only become important when food is in restricted supply,[205] a condition that is unlikely to be experienced by athletes during travel or competition. Animal studies also suggest that hypercaloric diets may prevent adaptation to jet lag.[206]

It has also been suggested that the composition of meals can affect circadian rhythms.[207] In 1983, Ehret and Scanlon[208] suggested that re-entrainment can be enhanced by eating a protein-rich breakfast and a carbohydrate-rich evening meal upon arrival at the destination – the tyrosine released following a high-protein meal should increase arousal, and the increase in tryptophan following carbohydrate intake in the evening would have the opposite effect. However, Krauchi et al.[209] claimed that a high carbohydrate intake in the morning could cause circadian phase advance, compared with carbohydrate meals in the evening. This appears to be linked more to the overall energy provision rather than specific nutrient effects.

An extension of the diet suggested by Ehret and Scanlon,[208] the Argonne diet, has also gained favour with some athletes and teams. In this programme, days of intake of high-protein foods alternate with days of fasting on small amounts of low-carbohydrate foods, including a fast before arrival, followed by a high-protein meal at the destination breakfast time.[210,211] This could possibly simulate the restricted feeding schedules in animal models shown to unmask the food-entrainable clock. However, to date, only a single clinical trial has been published on this diet in 2002[212] and although it was shown to successfully reduce jet lag symptoms in military personnel travelling between the US and Korea, no further studies appear to have been published on this technique.

Overall, the effect of dietary interventions on jet lag seem to be small,[5] and other alternatives to promote adjustment may be considered more effective; although, animal studies have shown that food-based entrainment may enhance adaptation of peripheral clocks, such as in the liver,[213,214] which are difficult to entrain through light or sleep, and which account for many of the physiological symptoms of jet lag. Further research is needed to definitively establish the role of diet in jet lag adaptation.

2.6 Pre-Adjustment

One of the best ways to avoid jet lag is to adapt to the new time zone before arrival at a destination. All the above zeitgebers can be used to precondition athletes to the new time zone before travel commences[17] (see the case studies in section 4 and figure 6).

In practice, it is easiest to effect small shifts in the circadian clock over time, rather than to induce a rapid large pre-adjustment and risk suffering jet lag before the trip.[154,215] A pre-adaptation shift of 9 hours in core temperature, melatonin secretion and sleep has been successfully achieved using exposure to light delayed by 3 hours per day in semi-controlled laboratory conditions,[17] and using light and melatonin in astronauts.[154,216] The case for melatonin pre-adjustment alone is less clear.[174,175] Slow adjustment schedules also allow participants to avoid any potential risks, such as increased cancer rates associated with exposure to light at night,[70-72] and heart and circulatory problems associated with eating during physiological night.[217]

However, these techniques require strict compliance and avoidance of inappropriate stimuli, and limit normal behaviour and social life for some time before travel.[141] In particular, adjustment to large time-zone differences requires dedication to eat and sleep during the physiological and environmental night.[215] Inadvertent single exposure to zeitgeber cues, such as light, can quickly result in readjustment to baseline conditions. In practice, adaptations of more than 1–2 hours per day for 3 days are unlikely to be practicable, given socioenvironmental constraints, and research has shown no clear benefit for adjustments of 2 hours versus 1 hour per day.[215]

In situations where performance is critically required, such as during the Olympic Games, pre-flight adaptation would be desirable. In practice, a combination of pre- and post-flight adaptation, depending on the length of time of the stay, seem to provide the optimum solution.

3. Other Factors to Consider

3.1 Effects of Flight versus Jet Lag

It is also important to consider the effects of long-distance travel in its own right on health, such as dehydration and fatigue.[144] All of these strategies work best in a well rested individual, rather than a sleep-deprived one, and the most important factor in adjusting to the destination time zone is adequate sleep. Although airline companies are constantly improving the design of their cabins and seats to improve comfort, sleep during a long-haul flight is likely to be fragmented at best. The recommendations given in section 2.2 on light exposure can be applied during the flight to improve adaption at the destination, but despite advice to adjust as quickly as possible to destination meal times, it is not recommended to eat meals at inappropriate times, such as during the biological ‘home’ night, as these can cause increased risk of heart disease.[217] Alcohol should also be avoided as it will increase dehydration. Travelling first or business class will provide the best conditions for uninterrupted sleep and adaptation measures, but the expense precludes this as a widespread strategy.

3.2 Individual Variability

It is critical to remember that any general advice on jet lag strategies and timings can only assume an average circadian clock phase, cycle length, and direction and rate of adaptation. In fact, large individual differences in these factors have been reported for many years, even in controlled experiments using markers such as core temperature[13-15] and the melatonin metabolite 6-sulphatoxymelatonin.[16] For example, in the latter study, only one of seven subjects adapted to an 8-hour eastward time-zone change by phase-delay. In a simulated 9-hour eastward change, Samel et al.[13] found that three of eight subjects adapted by delay and the remainder by advance. This can be seen even when subjects are carefully synchronized before the time shift.[17] Other studies have reported similar ratios for ten time zones.[18] Variable speeds of adaptation were also seen in all these studies.

It has been suggested that individuals may adjust to jet lag by adjusting the internal clock in different directions depending on their evening-morning preference or ‘chronotype’,[12] with ‘morning-type’ people whose circadian period is slightly shorter than 24 hours tending to advance, and evening-type people finding it easiest to adjust by delay.[139,218,219] Intermediate types showed highly variable responses.[220]

To plan an optimum adaptation strategy, these individual differences should ideally be taken into account, including each athlete’s internal phase. Some markers of circadian rhythm, such as body temperature and ‘clock’ gene expression, correlate with specific phases of the PRC; for example, core-temperature is around its lowest at the light PRC crossover and PRCs have been plotted relative to sleep timings,[138] to make them more generally accessible; however, at present, few systems are capable of easily monitoring these markers, therefore, the following advice covers the best practice currently available for the majority of people.

4. Case Studies

We will take as our case study examples, planned trips for the England Rugby Sevens squad for the HSBC Sevens Rugby World Cup Series in 2010/2011, and travel required for UK teams in the 2016 Summer Olympics in Rio de Janeiro, Brazil, but the suggestions described below are generally applicable to many sorts of trips.

4.1 Travel Across Three Time Zones Westwards: UK to Rio de Janeiro (–4 Hours Delay)

The 2016 Summer Olympics will take place in August, in Rio de Janeiro, Brazil. This trip involves a relatively modest change of 4 hours from the UK, as daylight savings time is in effect in the UK at this time; 01:00 in the UK would be equivalent to 21:00 on the previous day in Rio at the time of travel. Without any intervention, this trip would normally induce jet lag for approximately 2 days, as travel westwards is accommodated to approximately half a day per hour of time-zone change.

Standard medical advice might suggest that no adjustment should be made on such a trip if the duration of the stay were short, and that the travellers should maintain themselves on their home schedule. However, this advice is more suitable for businessmen than athletes, where business meeting times can be adjusted between mornings and afternoons to remain on home times. Competition times are not as flexible, and athletes are required to perform at their optimum physical and mental ability against other teams that are already adapted to local time zones.

It would therefore benefit travelling teams to schedule flights early to accommodate the 2–3 days of adjustment prior to competition. Although it would be theoretically possible to incorporate a pre-adjustment prior to the flight to stimulate adjustment in the correct direction, this would seem to involve a great deal of inconvenience in terms of light avoidance and sleep/wake time changes for relatively little benefit.

In this case, the best adjustment is a phase delay. To promote this adjustment on arrival following the PRC for light, the athlete should seek light at 15:00–22:00 Rio time, and avoid exposure to bright light at 22:00–09:00 Rio time (figure 4). These timings avoid the areas of weak effect at the borders of the PRC and times around the crossover point, which may show individual variation, leading to unwanted phase-advance effects. Here, because of the small time-zone difference, the overlap between the time of light avoidance and night-time in Rio is almost complete, although care should be taken with exposure to artificial electrical light, especially if the athlete wakes early as a result of jet lag. Sunglasses may be used, especially on arrival at the airport and in the mornings. Similarly, in this instance, the time of required light exposure coincides with the afternoon light at the destination.

Since jet lag is only expected for 2–3 days, these measures need only be employed for the first few days to promote phase delay. The PRCs are initially calculated according to the home

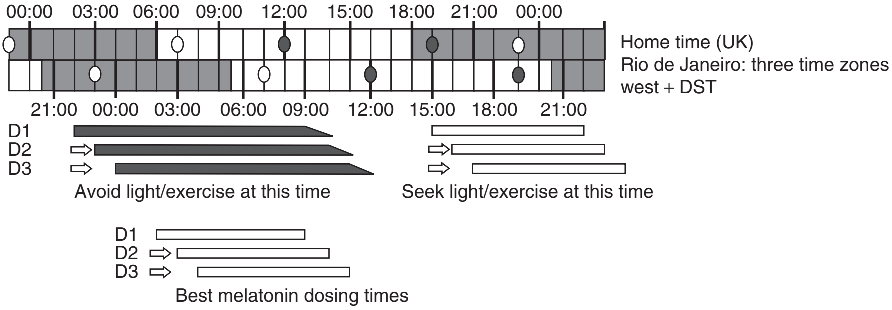

Fig. 4. Adaptation strategies. Case study 1: travel across three time zones westwards, for example from the UK to Rio de Janeiro, Brazil, in August, 2016 for the Summer Olympics (–4 h time difference as daylight savings time is in effect in the UK at this time). The time difference effects for this type of trip are shown in more detail in figure 1a. The upper section shows UK time; lower section shows time in Rio de Janeiro aligned with UK time to show the time difference and times of potential exposure to daylight following travel. Grey panels indicate night; white panels indicate daylight (taken from sunrise and sunset times in August, 2016); white ellipses show sleep and wake onset times, and black ellipses show meal times. Optimum times of exposure and avoidance to zeitgeber ('time-givers' in German) stimuli upon arrival are shown by black and white boxes. **DST** = daylight savings time; D1, 2 and 3 indicate days after arrival.

time zone; however, as adjustment gradually occurs to the new destination time, these windows of administration need to be shifted as well. For westwards travel, 1 hour should be added per day of adaptation until the new external conditions are fully adjusted to.

If melatonin is to be taken, the best time for administration would be 01:00–09:00 Rio time, to promote a phase delay whilst avoiding the crossover period. Melatonin should not be administered outside this period. However, the evidence for phase-delay effects of melatonin in humans is not strong[178] and, as the primary function of melatonin as a chronotherapeutic is to promote sleep, it should ideally only be taken in this instance, at the beginning of this time window at 01:00 Rio time. As this is 6 hours after the athlete's 'internal' sleep time, it is unlikely that they will still be awake at this time and it is unhelpful to wake them to administer a soporific agent, so melatonin is of limited use in this instance. It might be possible to take melatonin if the athlete wakes early on 'home' time to extend sleep (07:00 in the UK equates to 03:00 in Rio), but there is then a risk of carry-over effects of sleepiness in the daytime.[179]

The PRC for exercise is reported to be similar to that for light, albeit slightly delayed, so the same timings could be applied, as otherwise, with this small time-zone difference, optimum exercise timing would occur during both the 'internal' and destination night. According to the PRC, exercise should be avoided during the light avoidance zone. Although the evidence for effects of a food-clock on jet lag is inconclusive at present in humans, it would seem reasonable for this short adjustment to try to adapt meal times to local times either upon arrival or slowly shifting over the first few days.

4.2 Travel Across Four Time Zones Eastwards: UK to Dubai (+4 Hours in Advance)

The first leg of the HSBC Sevens Rugby World Cup series usually takes place in Dubai in December. Again, this trip involves a relatively modest change of 4 hours from the UK; 01:00 in the UK is equivalent to 05:00 in Dubai at the time of travel. Without any intervention, this trip would normally induce jet lag for approximately 4 days, as travel eastwards is accommodated to approximately 1 day per hour of time-zone change.

It would therefore, again, benefit teams to schedule flights as early as possible to accommodate the 4–5 days of adjustment prior to match day and, possibly, to incorporate a pre-adjustment prior to the flight to stimulate adjustment in the correct direction.

Upon arrival, the best adjustment in this case is a phase advance. To promote this, following the PRC for light, the athlete should avoid light between 23:00 and 10:00 in Dubai and seek exposure to bright light between 10:00 and 16:00 Dubai time, avoiding the crossover point where individual variation may alter the effect and the areas of weakest phase effect (figure 5a). If melatonin is to be taken, the best time for administration is between 14:00 and 20:00 to promote a phase-advance. The PRC for exercise is reported to be similar to that of light, although somewhat delayed and, in this instance, the same timings would apply and a shift in meal timings to local times should be attempted. This may be aided by the shifts in wake times, although athletes may find it hard to eat main meals earlier in the day when they do not necessarily feel hungry, therefore gradual shifts in times may be easier.

The PRCs are initially calculated according to the home time zone; however, as adjustment gradually occurs to the new destination time zone, these windows of administration need to be shifted. For eastwards travel, 1 hour should be subtracted for each day of adaptation until the new external conditions are fully adjusted to.

A pre-adjustment to promote adaptation before travel, in the direction of phase advance in this case, would involve adjusting the wake and sleep times to gradually bring them in line with the normal sleep-wake times for the destination. In this case, wake time should be brought forward earlier by 30–60 minutes every day prior to departure, and sleep onset time brought forward earlier as well (figure 5b). In this way, wake time is adjusted from the athlete's normal time of 07:00–06:00, then to 05:00 for 2 nights prior to departure, and to 04:00 the night before departure.

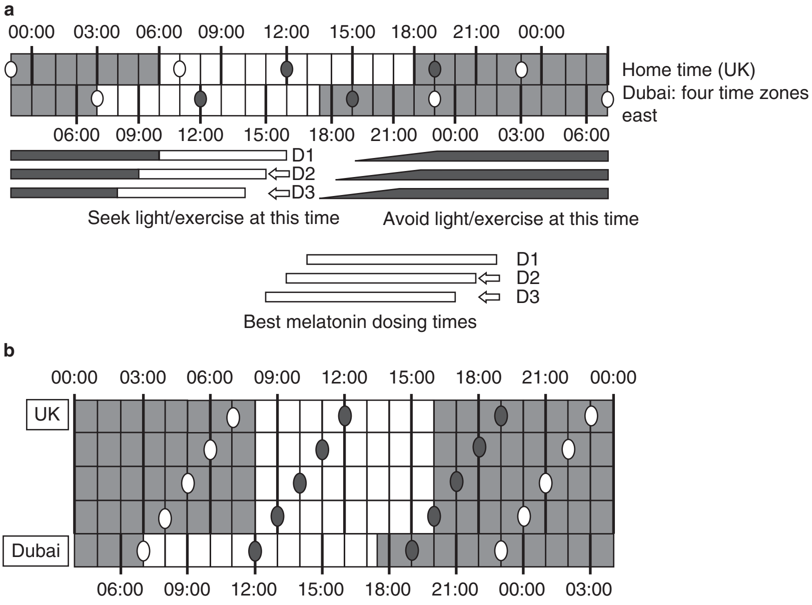

Fig. 5. Case study 2. (**a**) Travel across four time zones eastwards from the UK to Dubai, December 2010 (+4 h time difference). The time difference effects for this type of trip are shown in more detail in figure 1b. The upper section shows UK time; lower section shows time in Dubai aligned with UK time to show time difference and times of potential exposure to daylight following travel. Grey panels indicate night; white panels indicate daylight (taken from sunrise and sunset times in December, 2010; no daylight savings time is in force in either country at this time); white ellipses show sleep and wake onset times, and black ellipses show meal times. D1, 2 and 3 indicate days after arrival. Optimum times of exposure and avoidance to zeitgeber stimuli upon arrival are shown by black and white boxes. (**b**) The results of pre-adaptation strategy on times of sleep/wake onset (white ellipses) and meal times (black ellipses) are shown (refer to figure 5a for definitions of panels etc.).

This leaves the final adjustment to occur upon arrival. It is usually easier to adjust to an earlier wake time than to attempt to sleep at an earlier-than-normal time, and the ease of acceptance of this strategy may also depend on the chronotype of the athlete, with 'morning types' adapting more easily to this phase advance. Meal times can also be adjusted in the same way, although this requires more commitment. The same pre-adaptation strategy can be employed in the opposite direction for westward travel, and this strategy may be more easily adopted by 'evening-type' athletes.

Pre-adaptation strategies should be used in conjunction with the light avoidance/exposure times described in sections 2.2 and 2.6 for best effect. In this instance, light exposure pre-adaptation prior to travel is more tricky – sunrise does not occur until around 08:00 in the UK in December and should therefore be supplemented with electric light or possibly specialized light boxes. Light avoidance is less of an issue, as sunset occurs at 16:00 in the UK, leaving only 1 hour of overlap where natural light should be avoided. However, avoidance of artificial light will be more problematic and will require either the wearing of dark glasses or commitment to pre-adaptation. In this instance, a pre-adaptation strategy of 30 minutes instead of 1 hour may be more acceptable.

4.3 Multiple Trips: UK–New Zealand–USA

For the first leg of this trip, at the time of the HSBC Sevens Rugby World Cup in 2011, New Zealand is the only country that will be on daylight savings time, so this trip incurs the maximum time-zone difference possible of 13 hours; 01:00 in the UK is equivalent to 14:00 on the same day in New Zealand.

Although the standard rule of thumb suggests that this trip would cause 13 days of jet lag, assuming that travel would be eastwards from the

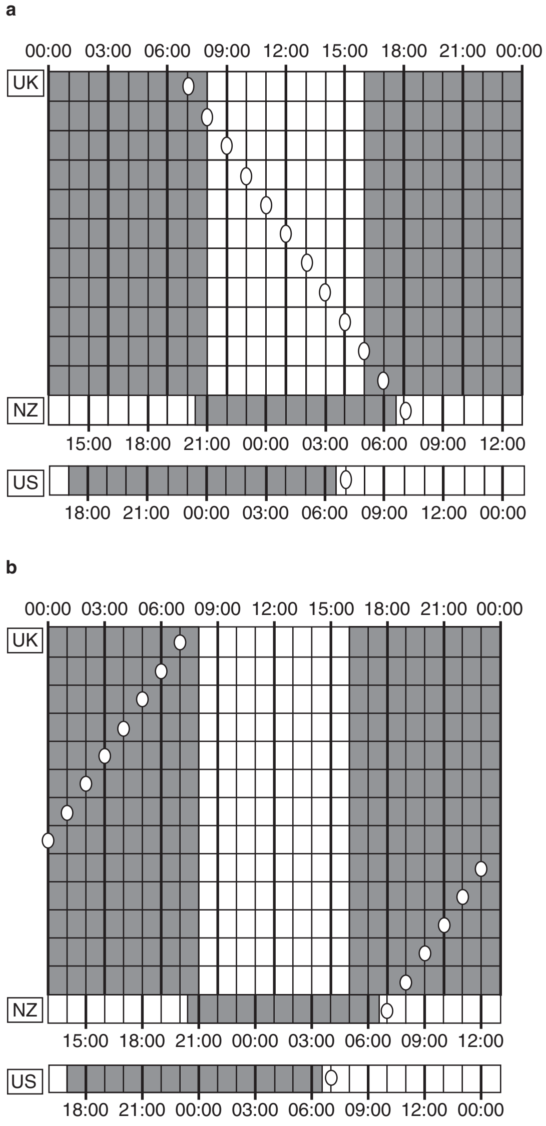

Fig. 6. Case study 3. Multiple trip travel across 12 time-zones eastwards from the UK to New Zealand, February, 2011 (+13 h time difference [the time difference effects for this type of trip are shown in more detail in figure 1c]). The upper line shows UK time; lower lines show time in New Zealand and the US aligned with UK time to show the time difference and times of potential exposure to daylight following travel. Grey panels indicate night, white panels indicate daylight (taken from sunrise and sunset times in February 2011; daylight savings time is in force in New Zealand at this time); white ellipses show sleep and wake onset times and black ellipses show meal times. Adjustment to the new time zone by advance or delay of the circadian clock can affect the length of time of suboptimal athletic performance. Adjustment to travel from the UK to New Zealand can be adjusted to in (**a**) 11 days by phase delay; whereas (**b**) adjustment takes 13 days by phase advance.

UK via Dubai, Singapore or Hong Kong. However, in practice, it would be likely that such a large time-zone change be would be adjusted to by advance as much as by delay, and the effect of the direction of travel is, therefore, probably nominal.

It would be slightly more efficient if the athlete's circadian system could treat this as 11 hours of delay, instead of 13 hours of advance and adjust accordingly, reducing the duration of jet lag slightly (figures 6a and b). In actuality, great variations are seen in the direction and length of adjustment to this sort of circadian disruption, and these can vary from person to person and also from trip to trip for the same person. Some research has suggested that the direction of adjustment is affected by the normal evening/morning preference of the individual, with 'evening-type' people showing a preference for phase delay in accordance with their longer circadian rhythms; personal preference will play a large part in both ease of adaptation and willingness to make the necessary environmental changes.

If adjustment proceeds in the direction of a phase advance, then the advice given in section 4.2 can be applied, with times adjusted for New Zealand, to promote a phase advance following an initial pre-flight adaptation. Assuming 3 days of prior adaptation (placing the athlete at day 3 of the adjusted time in figure 5a), this would give the result of needing to seek light exposure between 17:00 and 23:00 New Zealand-time, and avoid light during most of the day from 05:00 to 17:00, with similar requirements for exercise. This is unlikely to be practicable without careful management and rigorous sequestering from outside environmental conditions. Melatonin PRC timings are equally impractical, with best dosing times falling at 00:00 or a pre-adjusted internal time of around 08:00–09:00.

If adjustment occurs by phase delay, environmental factors are more manageable, as the advice given in section 4.1 should be applied, giving adjusted destination times for light exposure of 10:00–16:00, covering the brightest midday sunlight times, and light avoidance times of 16:00–04:00 so tactics, such as using sunglasses and only dim electric lighting, should be employed during the afternoon and evening. Melatonin dosing times are also more practical, from 21:00 to 03:00 after pre-adaptation.

It is therefore very much in the interest of the individual athlete, and of the team as a whole, to use pre-adjustment strategies to influence the direction of adjustment prior to travel (see section 4.2).

This trip is further complicated by the subsequent stage of competition, where a team travels to Las Vegas, NV, USA, which is –21:00 hours delayed relative to New Zealand time or 4 hours in advance. The timing between games is barely sufficient to allow players to fully adjust to local New Zealand times, if they adjust in the most efficient way by phase delay. However, if the player has adjusted in this direction, they are then at a disadvantage in adjusting to the new USA time zone, as this may mean that they will continue to adjust by phase delay, leading to 21 days of adjustment, rather than the 3 days of adjustment possible by phase advance (figures 6a and b).

In this instance, it may be possible to try to implement a reversal of the phase shift, using a second pre-adaptation strategy whilst in New Zealand, to try to force the body clocks of athletes to shift in the optimum direction. While it has been described in the literature that these reversals of phase shift can occur naturally under controlled conditions,[220] there is little to no literature on inducing them deliberately.

5. Conclusions

In this review, we have detailed potential strategies that athletes and teams can adopt in order to promote quick adaptation and minimize the effects

Table I. Practice points

Practice timepoints	Interventions	Rationale
Prior to travel	Education	Information regarding jet lag can usefully be provided to athletes to inform them of the symptoms and effects on athletic performance, to allow them to recognize these effects and to adjust their training and schedules accordingly; this is key as many athletes may dismiss the effects
	Pre-adjustment	This can be considered for large time-zone differences. It involves gradually shifting the sleep and eating schedule by 30–60 min each day towards the destination time for a few days prior to departure, accompanied by appropriately timed light avoidance and exposure
During travel	Minimize flight effects	Athletes should attempt to minimize the dehydrating effects of flight by drinking plenty of non-alcoholic fluids and by performing regular stretches to prevent muscle stiffness
On arrival	Light	Light is the most potent adjustment stimulus for the circadian clock; however, it has different effects on the clock at different times of day, so careful planning is required to gain the most benefit. In general, light has the greatest effects when the circadian clock is not expecting to encounter it, i.e. during the night. Light exposure in the early evening and first part of the night (on home, not destination time) induces adjustment by causing a phase delay that is required to reset the body clock following westward travel; whereas, exposure to light in the second half of the night and early morning (home, not local time) will cause an advance in the circadian phase that is required for adjustment to eastward travel
	Melatonin	Melatonin is a natural chemical produced by the body around the time of normal sleep onset and is thought to promote sleep, among other functions. It can be ingested to promote adaptation but caution should be taken, as it is not currently licensed for use in some countries, and care should be taken to obtain a high-quality formulation of known dose without any adulterants. Timing of ingestion also needs to be carefully calculated according to the PRC in order to avoid carry-over effects of drowsiness during the day because of mistimed or too large doses
	Exercise	Athletes should consider avoiding heavy training for the first few days after a long flight, while the effects of jet lag are at their most severe. Further research is required to establish the optimum time, amount and type of exercise needed to effect resetting of the circadian clock. However, since athletes are likely to be engaging in physical exercise as part of their normal training, exercise could be employed following the same recommendations and timings as those for light, to gain any potential enhancement in clock resetting and to avoid any potentially detrimental effects
	Food intake	Further research is also required to investigate the effects, if any, of diet and meal timing in jet lag adjustment in athletes, but a shift in meal timings to local time is likely to be beneficial to aid prompt adjustment, whether immediate or gradual

of jet lag on performance using these cues (table I). Athletes are particularly susceptible to jet lag, as they are often required to travel for long distances and then compete at their peak performance at times that are very different to their internal body-clock timings. Optimal performance also requires coordination of many physiological systems that are sensitive to jet lag disruption, as they are regulated by the circadian clock. However, the key to jet lag lies in its very nature; although symptoms arise because the circadian clock is misaligned with external conditions following transmeridian travel, the clock is inherently designed to adapt to those conditions, through entrainment to cues including light, hormones such as melatonin, food and exercise (table I).

Acknowledgements

Support for the preparation of this manuscript was provided by UK Sport and the Engineering and Physical Sciences Research Council of the United Kingdom. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Text rev. 4th ed. Washington, DC: American Psychiatric Association, 2000
2. WHO. International statistical classification of diseases and related health problems. 10th rev. 2nd ed. Geneva: World Health Organization, 2004
3. Jackson G. Come fly with me: jet lag and melatonin. Int J Clin Prac 2010 Jan; 64 (2): 135
4. Shneerson JM. Sleep medicine: a guide to sleep and its disorders. 2nd ed. Oxford: Blackwell, 2005
5. Waterhouse J, Reilly T, Atkinson G, et al. Jet lag: trends and coping strategies. Lancet 2007 Mar 31; 369 (9567): 1117-29
6. Hastings M, O'Neill JS, Maywood ES. Circadian clocks: regulators of endocrine and metabolic rhythms. J Endocrinol 2007 Nov; 195 (2): 187-98
7. Albrecht U, Eichele G. The mammalian circadian clock. Curr Opin Genet Dev 2003 Jun; 13 (3): 271-7
8. Czeisler CA, Duffy JF, Shanahan TL, et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. Science 1999; 284 (5423): 2177-81
9. Middleton B, Arendt J, Stone BM. Human circadian rhythms in constant dim light (8 lux) with knowledge of clock time. J Sleep Res 1996; 5 (2): 69-76
10. Scheer FA, Wright Jr KP, Kronauer RE, et al. Plasticity of the intrinsic period of the human circadian timing system. PLoS One 2007; 2 (1): e721
11. Eastman CI, Burgess HJ. How to travel the world without jet lag. Sleep Med Clin 2009; 4 (2): 241-55
12. Manfredini R, Manfredini F, Fersini C, et al. Circadian rhythms, athletic performance, and jet lag. Br J Sports Med 1998; 32 (2): 101-6
13. Samel A, Wegmann HM, Vejvoda M, et al. Influence of melatonin treatment on human circadian rhythmicity before and after a simulated 9-hr time shift. J Biol Rhythms 1991; 6 (3): 235-48
14. Gander PH, Kronauer RE, Graeber RC. Phase shifting two coupled circadian pacemakers: implications for jet lag. Am J Physiol 1985; 249 (6 Pt 2): R704-19
15. Gundel A, Wegmann HM. Transition between advance and delay responses to eastbound transmeridian flights. Chronobiol Int 1989; 6 (2): 147-56
16. Arendt J, Aldhous M, Marks V. Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial. Br Med J (Clin Res Ed) 1986; 292 (6529): 1170
17. Deacon S, Arendt J. Adapting to phase shifts, I: an experimental model for jet lag and shift work. Physiol Behav 1996; 59 (4-5): 665-73
18. Winfree AT. The geometry of biological time. 2nd ed. New York, London: Springer, 2001
19. Heggie TW. Traveling to Canada for the Vancouver 2010 Winter Olympic and Paralympic Games. Travel Med Infect Dis 2009; 7 (4): 207-11
20. Arendt J, Stone B, Skene DJ. Sleep disruption in jet lag and other circadian rhythm disturbances. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 4th ed. Philadelphia, (PA), Edinburgh: Elsevier Saunders, 2005: 659-72
21. Haimov I, Arendt J. The prevention and treatment of jet lag. Sleep Med Rev 1999 Sep; 3 (3): 229-40
22. Williams RL, Karacan I, Moore CA, editors. Sleep disorders: diagnosis and treatment. 2nd ed. New York (NY): Wiley; 1988
23. Sack RL. The pathophysiology of jet lag. Travel Med Infect Dis 2009; 7 (2): 102-10
24. Touzet S, Rabilloud M, Boehringer H, et al. Relationship between sleep and secretion of gonadotropin and ovarian hormones in women with normal cycles. Fertil Steril 2002; 77 (4): 738-44
25. Baumgartner A, Dietzel M, Saletu B, et al. Influence of partial sleep deprivation on the secretion of thyrotropin, thyroid hormones, growth hormone, prolactin, luteinizing hormone, follicle stimulating hormone, and estradiol in healthy young women. Psychiatry Res 1993 Aug; 48 (2): 153-78
26. Reilly T, Waterhouse J. Sports performance: is there evidence that the body clock plays a role? Eur J Appl Physiol 2009; 106 (3): 321-32
27. Winget CM, DeRoshia CW, Holley DC. Circadian rhythms and athletic performance. Med Sci Sports Exerc 1985; 17 (5): 498-516
28. Guette M, Gondin J, Martin A. Time-of-day effect on the torque and neuromuscular properties of dominant and non-dominant quadriceps femoris. Chronobiol Int 2005; 22 (3): 541-58
29. Nicolas A, Gauthier A, Bessot N, et al. Time-of-day effects on myoelectric and mechanical properties of muscle

during maximal and prolonged isokinetic exercise. Chronobiol Int 2005; 22 (6): 997-1011

30. Sedliak M, Finni T, Cheng S, et al. Effect of time-of-day-specific strength training on serum hormone concentrations and isometric strength in men. Chronobiol Int 2007; 24 (6): 1159-77
31. Wyse JP, Mercer TH, Gleeson NP. Time-of-day dependence of isokinetic leg strength and associated interday variability. Br J Sports Med 1994; 28 (3): 167-70
32. Souissi N, Gauthier A, Sesboue B, et al. Circadian rhythms in two types of anaerobic cycle leg exercise: force-velocity and 30-s Wingate tests. Int J Sports Med 2004; 25 (1): 14-9
33. Gauthier A, Davenne D, Martin A, et al. Diurnal rhythm of the muscular performance of elbow flexors during isometric contractions. Chronobiol Int 1996; 13 (2): 135-46
34. Nicolas A, Gauthier A, Trouillet J, et al. The influence of circadian rhythm during a sustained submaximal exercise and on recovery process. J Electromyogr Kinesiol 2008; 18 (2): 284-90
35. Souissi N, Bessot N, Chamari K, et al. Effect of time of day on aerobic contribution to the 30-s Wingate test performance. Chronobiol Int 2007; 24 (4): 739-48
36. Reilly T, Down A. Investigation of circadian rhythms in anaerobic power and capacity of the legs. J Sports Med Phys Fitness 1992; 32 (4): 343-7
37. Martin L, Doggart AL, Whyte GP. Comparison of physiological responses to morning and evening submaximal running. J Sports Sci 2001; 19 (12): 969-76
38. Arnett MG. Effects of prolonged and reduced warm-ups on diurnal variation in body temperature and swim performance. J Strength Cond Res 2002; 16 (2): 256-61
39. Baxter C, Reilly T. Influence of time of day on all-out swimming. Br J Sports Med 1983; 17 (2): 122-7
40. Martin L, Thompson K. Reproducibility of diurnal variation in sub-maximal swimming. Int J Sports Med 2000; 21 (6): 387-92
41. Atkinson G, Reilly T. Effects of age and time of day on preferred work rates during prolonged exercise. Chronobiol Int 1995; 12 (2): 121-34
42. Atkinson G, Todd C, Reilly T, et al. Diurnal variation in cycling performance: influence of warm-up. J Sports Sci 2005; 23 (3): 321-9
43. Bessot N, Nicolas A, Moussay S, et al. The effect of pedal rate and time of day on the time to exhaustion from high-intensity exercise. Chronobiol Int 2006; 23 (5): 1009-24
44. Deschenes MR, Kraemer WJ, Bush JA, et al. Biorhythmic influences on functional capacity of human muscle and physiological responses. Med Sci Sports Exerc 1998; 30 (9): 1399-407
45. Giacomoni M, Billaut F, Falgairette G. Effects of the time of day on repeated all-out cycle performance and short-term recovery patterns. Int J Sports Med 2006; 27 (6): 468-74
46. Racinais S, Blonc S, Jonville S, et al. Time of day influences the environmental effects on muscle force and contractility. Med Sci Sports Exerc 2005; 37 (2): 256-61
47. Racinais S, Connes P, Bishop D, et al. Morning versus evening power output and repeated-sprint ability. Chronobiol Int 2005; 22 (6): 1029-39
48. Reilly T, Atkinson G, Edwards B, et al. Diurnal variation in temperature, mental and physical performance, and tasks specifically related to football (soccer). Chronobiol Int 2007; 24 (3): 507-19
49. Drust B, Waterhouse J, Atkinson G, et al. Circadian rhythms in sports performance: an update. Chronobiol Int 2005; 22 (1): 21-44
50. Hayes LD, Bickerstaff GF, Baker JS. Interactions of cortisol, testosterone, and resistance training: influence of circadian rhythms. Chronobiol Int 2010; 27 (4): 675-705
51. O'Connor PJ. FIMS position statement: air travel and performance in sports. 2004 [online]. Available from URL: http://www.fims.org [Accessed 2011 Dec 10]
52. Bullock N, Martin DT, Ross A, et al. Effect of long haul travel on maximal sprint performance and diurnal variations in elite skeleton athletes. Br J Sports Med 2007; 41 (9): 569-73; discussion 73
53. O'Connor PJ, Morgan WP, Koltyn KF, et al. Air travel across four time zones in college swimmers. J Appl Physiol 1991; 70 (2): 756-63
54. Reilly T, Atkinson G, Budgett R. Effect of low-dose temazepam on physiological variables and performance tests following a westerly flight across five time zones. Int J Sports Med 2001; 22 (3): 166-74
55. Lemmer B, Kern RI, Nold G, et al. Jet lag in athletes after eastward and westward time-zone transition. Chronobiol Int 2002; 19 (4): 743-64
56. Bishop D. The effects of travel on team performance in the Australian national netball competition. J Sci Med Sport 2004; 7 (1): 118-22
57. Jehue R, Street D, Huizenga R. Effect of time zone and game time changes on team performance: National Football League. Med Sci Sports Exerc 1993; 25 (1): 127-31
58. Smith RS, Guilleminault C, Efron B. Circadian rhythms and enhanced athletic performance in the National Football League. Sleep 1997; 20 (5): 362-5
59. Steenland K, Deddens JA. Effect of travel and rest on performance of professional basketball players. Sleep 1997; 20 (5): 366-9
60. Meney I, Waterhouse J, Atkinson G, et al. The effect of one night's sleep deprivation on temperature, mood, and physical performance in subjects with different amounts of habitual physical activity. Chronobiol Int 1998; 15 (4): 349-63
61. Van Dongen HP, Dinges DF. Sleep, circadian rhythms, and psychomotor vigilance. Clin Sports Med 2005; 24 (2): 237-49, vii-viii
62. Kang JE, Lim MM, Bateman RJ, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 2009; 326 (5955): 1005-7
63. Blumert PA, Crum AJ, Ernsting M, et al. The acute effects of twenty-four hours of sleep loss on the performance of national-caliber male collegiate weightlifters. J Strength Cond Res 2007; 21 (4): 1146-54
64. Scott AJ. Shift work and health. Prim Care 2000; 27 (4): 1057-79
65. Knutsson A. Health disorders of shift workers. Occup Med (Lond) 2003; 53 (2): 103-8
66. Cho K, Ennaceur A, Cole JC, et al. Chronic jet lag produces cognitive deficits. J Neurosci 2000; 20 (6): RC66 (1-5)

67. Katz G, Durst R, Zislin Y, et al. Psychiatric aspects of jet lag: review and hypothesis. Med Hypotheses 2001; 56 (1): 20-3
68. Turek FW. From circadian rhythms to clock genes in depression. Int Clin Psychopharmacol 2007; 22 Suppl. 2: S1-8
69. Mahoney MM. Shift work, jet lag, and female reproduction. Int J Endocrinol. Epub 2010 Mar 8
70. Moser M, Schaumberger K, Schernhammer E, et al. Cancer and rhythm. Cancer Causes Control 2006; 17 (4): 483-7
71. Filipski E, King VM, Li X, et al. Disruption of circadian coordination accelerates malignant growth in mice. Pathol Biol (Paris) 2003; 51 (4): 216-9
72. Filipski E, Delaunay F, King VM, et al. Effects of chronic jet lag on tumor progression in mice. Cancer Res 2004; 64 (21): 7879-85
73. Davidson AJ, Sellix MT, Daniel J, et al. Chronic jet-lag increases mortality in aged mice. Curr Biol 2006; 16 (21): R914-6
74. Stevens RG. Working against our endogenous circadian clock: breast cancer and electric lighting in the modern world. Mutat Res 2009; 680 (1-2): 106-8
75. Davis S, Mirick DK. Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle. Cancer Causes Control 2006; 17 (4): 539-45
76. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. J Natl Cancer Inst 2001; 93 (20): 1557-62
77. Kojo K, Pukkala E, Auvinen A. Breast cancer risk among Finnish cabin attendants: a nested case-control study. Occup Environ Med 2005; 62 (7): 488-93
78. Fu L, Lee CC. The circadian clock: pacemaker and tumour suppressor. Nat Rev Cancer 2003; 3 (5): 350-61
79. Cho K. Chronic 'jet lag' produces temporal lobe atrophy and spatial cognitive deficits. Nat Neurosci 2001; 4 (6): 567-8
80. Reilly T, Edwards B. Altered sleep-wake cycles and physical performance in athletes. Physiol Behav 2007; 90 (2-3): 274-84
81. Gallego M, Virshup DM. Post-translational modifications regulate the ticking of the circadian clock. Nat Rev Mol Cell Biol 2007; 8 (2): 139-48
82. Gekakis N, Staknis D, Nguyen HB, et al. Role of the CLOCK protein in the mammalian circadian mechanism. Science 1998; 280 (5369): 1564-9
83. Hogenesch JB, Gu YZ, Jain S, et al. The basic-helix-loop-helix-PAS orphan MOP3 forms transcriptionally active complexes with circadian and hypoxia factors. Proc Natl Acad Sci U S A 1998; 95 (10): 5474-9
84. Honma S, Ikeda M, Abe H, et al. Circadian oscillation of BMAL1, a partner of a mammalian clock gene Clock, in rat suprachiasmatic nucleus. Biochem Biophys Res Commun 1998; 250 (1): 83-7
85. Shearman LP, Zylka MJ, Weaver DR, et al. Two period homologs: circadian expression and photic regulation in the suprachiasmatic nuclei. Neuron 1997; 19 (6): 1261-9
86. Shigeyoshi Y, Taguchi K, Yamamoto S, et al. Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer1 transcript. Cell 1997; 91 (7): 1043-53
87. Zylka MJ, Shearman LP, Weaver DR, et al. Three period homologs in mammals: differential light responses in the suprachiasmatic circadian clock and oscillating transcripts outside of brain. Neuron 1998; 20 (6): 1103-10
88. Ceriani MF, Darlington TK, Staknis D, et al. Light-dependent sequestration of TIMELESS by CRYPTOCHROME. Science 1999; 285 (5427): 553-6
89. Griffin Jr EA, Staknis D, Weitz CJ. Light-independent role of CRY1 and CRY2 in the mammalian circadian clock. Science 1999; 286 (5440): 768-71
90. BioCarta. Pathways: circadian rhythms [online]. Available from URL: http://www.biocarta.com/pathfiles/m_circadianPathway.asp [Accessed 2011 Nov 14]
91. Gachon F, Nagoshi E, Brown SA, et al. The mammalian circadian timing system: from gene expression to physiology. Chromosoma 2004; 113 (3): 103-12
92. Hofstra WA, de Weerd AW. How to assess circadian rhythm in humans: a review of literature. Epilepsy Behav 2008; 13 (3): 438-44
93. Weinert D. Circadian temperature variation and ageing. Ageing research reviews 2009; 9 (1): 51-60
94. Hsu DS, Zhao X, Zhao S, et al. Putative human blue-light photoreceptors hCRY1 and hCRY2 are flavoproteins. Biochemistry 1996; 35 (44): 13871-7
95. Zhang EE, Liu AC, Hirota T, et al. A genome-wide RNAi screen for modifiers of the circadian clock in human cells. Cell 2009; 139 (1): 199-210
96. Zheng B, Albrecht U, Kaasik K, et al. Nonredundant roles of the mPer1 and mPer2 genes in the mammalian circadian clock. Cell 2001; 105 (5): 683-94
97. Zhu Y, Stevens RG, Leaderer D, et al. Non-synonymous polymorphisms in the circadian gene NPAS2 and breast cancer risk. Breast Cancer Res Treat 2008; 107 (3): 421-5
98. Preitner N, Damiola F, Lopez-Molina L, et al. The orphan nuclear receptor REV-ERBalpha controls circadian transcription within the positive limb of the mammalian circadian oscillator. Cell 2002; 110 (2): 251-60
99. Sato TK, Panda S, Miraglia LJ, et al. A functional genomics strategy reveals Rora as a component of the mammalian circadian clock. Neuron 2004; 43 (4): 527-37
100. Eide EJ, Woolf MF, Kang H, et al. Control of mammalian circadian rhythm by CKIepsilon-regulated proteasome-mediated PER2 degradation. Mol Cell Biol 2005; 25 (7): 2795-807
101. Busino L, Bassermann F, Maiolica A, et al. SCFFbxl3 controls the oscillation of the circadian clock by directing the degradation of cryptochrome proteins. Science 2007; 316 (5826): 900-4
102. Shirogane T, Jin J, Ang XL, et al. SCFbeta-TRCP controls clock-dependent transcription via casein kinase 1-dependent degradation of the mammalian period-1 (Per1) protein. J Biol Chem 2005; 280 (29): 26863-72
103. Duffy JF, Dijk DJ, Hall EF, et al. Relationship of endogenous circadian melatonin and temperature rhythms to self-reported preference for morning or evening activity in young and older people. J Investig Med 1999; 47 (3): 141-50
104. Rollag MD, Berson DM, Provencio I. Melanopsin, ganglion-cell photoreceptors, and mammalian photoentrainment. J Biol Rhythms 2003; 18 (3): 227-34

105. Foster RG, Hankins MW. Circadian vision. Curr Biol 2007; 17 (17): R746-51
106. Foster RG. Neurobiology: bright blue times. Nature 2005; 433 (7027): 698-9
107. Thapan K, Arendt J, Skene DJ. An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. J Physiol 2001; 535 (Pt 1): 261-7
108. Brainard GC, Hanifin JP, Greeson JM, et al. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. J Neurosci 2001; 21 (16): 6405-12
109. Lucas RJ, Freedman MS, Munoz M, et al. Regulation of the mammalian pineal by non-rod, non-cone, ocular photoreceptors. Science 1999; 284 (5413): 505-7
110. Stephan FK, Zucker I. Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. Proc Natl Acad Sci U S A 1972; 69 (6): 1583-6
111. Whitmore D, Sassone-Corsi P, Foulkes NS. PASting together the mammalian clock. Curr Opin Neurobiol 1998; 8 (5): 635-41
112. Tosini G, Menaker M. Circadian rhythms in cultured mammalian retina. Science 1996; 272 (5260): 419-21
113. Plautz JD, Kaneko M, Hall JC, et al. Independent photoreceptive circadian clocks throughout Drosophila. Science 1997; 278 (5343): 1632-5
114. Fahrenkrug J, Georg B, Hannibal J, et al. Diurnal rhythmicity of the clock genes Per1 and Per2 in the rat ovary. Endocrinology 2006; 147 (8): 3769-76
115. Karman BN, Tischkau SA. Circadian clock gene expression in the ovary: effects of luteinizing hormone. Biol Reprod 2006; 75 (4): 624-32
116. Horard B, Rayet B, Triqueneaux G, et al. Expression of the orphan nuclear receptor ERRalpha is under circadian regulation in estrogen-responsive tissues. J Mol Endocrinol 2004; 33 (1): 87-97
117. Nakamura TJ, Moriya T, Inoue S, et al. Estrogen differentially regulates expression of Per1 and Per2 genes between central and peripheral clocks and between reproductive and nonreproductive tissues in female rats. J Neurosci Res 2005; 82 (5): 622-30
118. He PJ, Hirata M, Yamauchi N, et al. Up-regulation of Per1 expression by estradiol and progesterone in the rat uterus. J Endocrinol 2007; 194 (3): 511-9
119. Kennaway DJ. The role of circadian rhythmicity in reproduction. Hum Reprod Update 2005; 11 (1): 91-101
120. Gibbs JE, Beesley S, Plumb J, et al. Circadian timing in the lung; a specific role for bronchiolar epithelial cells. Endocrinology 2009; 150 (1): 268-76
121. Tanioka M, Yamada H, Doi M, et al. Molecular clocks in mouse skin. J Invest Derm 2009; 129 (5): 1225-31
122. Granados-Fuentes D, Tseng A, Herzog ED. A circadian clock in the olfactory bulb controls olfactory responsivity. J Neurosci 2006; 26 (47): 12219-25
123. Balsalobre A, Damiola F, Schibler U. A serum shock induces circadian gene expression in mammalian tissue culture cells. Cell 1998; 93 (6): 929-37
124. Reddy AB, Field MD, Maywood ES, et al. Differential resynchronisation of circadian clock gene expression within the suprachiasmatic nuclei of mice subjected to experimental jet lag. J Neurosci 2002; 22 (17): 7326-30
125. Yamazaki S, Numano R, Abe M, et al. Resetting central and peripheral circadian oscillators in transgenic rats. Science 2000; 288 (5466): 682-5
126. Sosniyenko S, Parkanova D, Illnerova H, et al. Different mechanisms of adjustment to a change of the photoperiod in the suprachiasmatic and liver circadian clocks. Am J Physiol Regul Integr Comp Physiol 2010; 298 (4): R959-71
127. Stokkan KA, Yamazaki S, Tei H, et al. Entrainment of the circadian clock in the liver by feeding. Science 2001; 291 (5503): 490-3
128. Mendoza J. Circadian clocks: setting time by food. J Neuroendocrinol 2007; 19 (2): 127-37
129. Khalsa SB, Jewett ME, Cajochen C, et al. A phase response curve to single bright light pulses in human subjects. J Physiol 2003; 549 (Pt 3): 945-52
130. Burgess HJ, Revell VL, Eastman CI. A three pulse phase response curve to three milligrams of melatonin in humans. J Physiol 2008; 586 (2): 639-47
131. Duffy JF, Czeisler CA. Effect of light on human circadian physiology. Sleep Med Clin 2009; 4 (2): 165-77
132. Czeisler CA, Kronauer RE, Allan JS, et al. Bright light induction of strong (type 0) resetting of the human circadian pacemaker. Science 1989; 244 (4910): 1328-33
133. Jewett ME, Rimmer DW, Duffy JF, et al. Human circadian pacemaker is sensitive to light throughout subjective day without evidence of transients. Am J Physiol 1997; 273 (5 Pt 2): R1800-9
134. Zeitzer JM, Dijk DJ, Kronauer R, et al. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. J Physiol 2000; 526 (Pt 3): 695-702
135. Duffy JF, Zeitzer JM, Czeisler CA. Decreased sensitivity to phase-delaying effects of moderate intensity light in older subjects. Neurobiol Aging 2007; 28 (5): 799-807
136. Deacon S, Arendt J. Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. Brain research 1995; 688 (1-2): 77-85
137. Paul MA, Miller JC, Gray GW, et al. Melatonin treatment for eastward and westward travel preparation. Psychopharmacology 2010; 208 (3): 377-86
138. Burgess HJ, Revell VL, Molina TA, et al. Human phase response curves to three days of daily melatonin: 0.5 mg versus 3.0 mg. J Clin Endocrinol Metab 2010 Jul; 95 (7): 3325-31
139. Duffy JF, Wright Jr KP. Entrainment of the human circadian system by light. J Biol Rhythms 2005; 20 (4): 326-38
140. Cain SW, Dennison CF, Zeitzer JM, et al. Sex differences in phase angle of entrainment and melatonin amplitude in humans. J Biol Rhythms 2010; 25 (4): 288-96
141. Arendt J. Managing jet lag: some of the problems and possible new solutions. Sleep Med Rev 2009; 13 (4): 249-56
142. Milner CE, Cote KA. Benefits of napping in healthy adults: impact of nap length, time of day, age, and experience with napping. J Sleep Res 2009; 18 (2): 272-81

143. Bes F, Jobert M, Schulz H. Modeling napping, post-lunch dip, and other variations in human sleep propensity. Sleep 2009; 32 (3): 392-8

144. Auger RR, Morgenthaler TI. Jet lag and other sleep disorders relevant to the traveler. Travel Med Infect Dis 2009; 7 (2): 60-8

145. Cook CJ, Crewther BT, Kilduff LP, et al. Skill execution and sleep deprivation: effects of acute caffeine or creatine supplementation-a randomized placebo-controlled trial. J Int Soc Sports Nutr 2011; 8 (2) 1-8

146. Pierard C, Beaumont M, Enslen M, et al. Resynchronization of hormonal rhythms after an eastbound flight in humans: effects of slow-release caffeine and melatonin. Eur J Appl Physiol 2001; 85 (1-2): 144-50

147. Beaumont M, Batejat D, Pierard C, et al. Caffeine or melatonin effects on sleep and sleepiness after rapid eastward transmeridian travel. J Appl Physiol 2004; 96 (1): 50-8

148. Burke LM. Caffeine and sports performance. Appl Physiol Nutr Metab 2008; 33 (6): 1319-34

149. Czeisler CA, Walsh JK, Roth T, et al. Modafinil for excessive sleepiness associated with shift-work sleep disorder. N Engl J Med 2005; 353 (5): 476-86

150. Agency TWA-D. The prohibited list. 2011 [online]. Available from URL: http://www.wada-ama.org/en/Science-Medicine/Prohibited-List [Accessed 2011 Nov 24]

151. Charles RB, Kirkham AJ, Guyatt AR, et al. Psychomotor, pulmonary and exercise responses to sleep medication. Br J Clin Pharmacol 1987; 24 (2): 191-7

152. Reilly T, Maughan R, Budgett R. Melatonin: a position statement of the British Olympic Association. Br J Sports Med 1998; 32 (2): 99-100

153. Wirz-Justice A, Krauchi K, Cajochen C, et al. Evening melatonin and bright light administration induce additive phase shifts in dim light melatonin onset. J Pineal Res 2004; 36 (3): 192-4

154. Revell VL, Burgess HJ, Gazda CJ, et al. Advancing human circadian rhythms with afternoon melatonin and morning intermittent bright light. J Clin Endocrinol Metab 2006; 91 (1): 54-9

155. Cagnacci A, Soldani R, Yen SS. Contemporaneous melatonin administration modifies the circadian response to nocturnal bright light stimuli. Am J Physiol 1997; 272 (2 Pt 2): R482-6

156. Cajochen C, Krauchi K, Danilenko KV, et al. Evening administration of melatonin and bright light: interactions on the EEG during sleep and wakefulness. J Sleep Res 1998; 7 (3): 145-57

157. Minors DS, Waterhouse JM, Wirz-Justice A. A human phase-response curve to light. Neurosci Lett 1991; 133 (1): 36-40

158. Samel A, Wegmann HM. Bright light: a countermeasure for jet lag? Chronobiol Int 1997; 14 (2): 173-83

159. Houpt TA, Boulos Z, Moore-Ede MC. MidnightSun: software for determining light exposure and phase-shifting schedules during global travel. Physiol Behav 1996; 59 (3): 561-8

160. Virgin Atlantic. Jet lag fighter [online]. Available from URL: http://www.virgin-atlantic.com/en/gb/bookflightsandmore/innovationzone/virginfamily/jetlagfighter.jsp [Accessed 2011 Nov 11]

161. Gronfier C, Wright Jr KP, Kronauer RE, et al. Efficacy of a single sequence of intermittent bright light pulses for delaying circadian phase in humans. Am J Physiol Endocrinol Metab 2004; 287 (1): E174-81

162. Boivin DB, Duffy JF, Kronauer RE, et al. Dose-response relationships for resetting of human circadian clock by light. Nature 1996; 379 (6565): 540-2

163. Lockley SW, Brainard GC, Czeisler CA. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. J Clin Endocrinol Metab 2003; 88 (9): 4502-5

164. Revell VL, Arendt J, Terman M, et al. Short-wavelength sensitivity of the human circadian system to phase-advancing light. J Biol Rhythms 2005; 20 (3): 270-2

165. Viola AU, James LM, Schlangen LJ, et al. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. Scand J Work Environ Health 2008; 34 (4): 297-306

166. Francis G, Bishop L, Luke C, et al. Sleep during the Antarctic winter: preliminary observations on changing the spectral composition of artificial light. J Sleep Res 2008; 17 (3): 354-60

167. Sasseville A, Paquet N, Sevigny J, et al. Blue blocker glasses impede the capacity of bright light to suppress melatonin production. J Pineal Res 2006; 41 (1): 73-8

168. Zawilska JB, Skene DJ, Arendt J. Physiology and pharmacology of melatonin in relation to biological rhythms. Pharmacol Rep 2009; 61 (3): 383-410

169. Rajaratnam SM, Middleton B, Stone BM, et al. Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. J Physiol 2004; 561 (Pt 1): 339-51

170. Brown GM, Pandi-Perumal SR, Trakht I, et al. Melatonin and its relevance to jet lag. Travel Med Infect Dis 2009; 7 (2): 69-81

171. Arendt J, Skene DJ. Melatonin as a chronobiotic. Sleep Med Rev 2005; 9 (1): 25-39

172. Arendt J. Does melatonin improve sleep? Efficacy of melatonin. BMJ 2006; 332 (7540): 550

173. Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders: an American Academy of Sleep Medicine report. Sleep 2007; 30 (11): 1445-59

174. Herxheimer A, Petrie KJ. Melatonin for preventing and treating jet lag. Cochrane Database Syst Rev 2001; (1): CD001520

175. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Cochrane Database Syst Rev 2002; (2): CD001520

176. Revell VL, Eastman CI. How to trick mother nature into letting you fly around or stay up all night. J Biol Rhythms 2005 Aug; 20 (4): 353-65

177. Lewy AJ, Bauer VK, Ahmed S, et al. The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. Chronobiol Int 1998; 15 (1): 71-83

178. Wirz-Justice A, Werth E, Renz C, et al. No evidence for a phase delay in human circadian rhythms after a single morning melatonin administration. J Pineal Res 2002; 32 (1): 1-5

179. Atkinson G, Jones H, Edwards BJ, et al. Effects of daytime ingestion of melatonin on short-term athletic performance. Ergonomics 2005; 48 (11-14): 1512-22
180. Tan DX, Hardeland R, Manchester LC, et al. The changing biological roles of melatonin during evolution: from an antioxidant to signals of darkness, sexual selection and fitness. Biol Rev Camb Philos Soc 2010; 85 (3): 607-23
181. Reiter RJ, Manchester LC, Fuentes-Broto L, et al. Cardiac hypertrophy and remodelling: pathophysiological consequences and protective effects of melatonin. J Hypertens 2010; 28 Suppl. 1: S7-12
182. European Medicines Agency. Circadin [online]. Available from URL: http://www.emea.europa.eu/humandocs/Humans/EPAR/circadin/circadin.htm [Accessed 2011 Nov 11]
183. Arendt J, Rajaratnam SM. Melatonin and its agonists: an update. Br J Psychiatry 2008; 193 (4): 267-9
184. Suhner A, Schlagenhauf P, Johnson R, et al. Comparative study to determine the optimal melatonin dosage form for the alleviation of jet lag. Chronobiol Int 1998; 15 (6): 655-66
185. Mistlberger RE. Scheduled daily exercise or feeding alters the phase of photic entrainment in Syrian hamsters. Physiol Behav 1991; 50 (6): 1257-60
186. Mistlberger RE. Effects of daily schedules of forced activity on free-running rhythms in the rat. J Biol Rhythms 1991; 6 (1): 71-80
187. Redlin U, Mrosovsky N. Exercise and human circadian rhythms: what we know and what we need to know. Chronobiol Int 1997; 14 (2): 221-9
188. Beersma DG, Hiddinga AE. No impact of physical activity on the period of the circadian pacemaker in humans. Chronobiol Int 1998; 15 (1): 49-57
189. Atkinson G, Fullick S, Grindey C, et al. Exercise, energy balance and the shift worker. Sports Med 2008; 38 (8): 671-85
190. Atkinson G, Edwards B, Reilly T, et al. Exercise as a synchroniser of human circadian rhythms: an update and discussion of the methodological problems. Eur J Appl Physiol 2007; 99 (4): 331-41
191. Baehr EK, Eastman CI, Revelle W, et al. Circadian phase-shifting effects of nocturnal exercise in older compared with young adults. Am J Physiol Regul Integr Comp Physiol 2003; 284 (6): R1542-50
192. Youngstedt SD, Kripke DF, Elliott JA. Circadian phase-delaying effects of bright light alone and combined with exercise in humans. Am J Physiol Regul Integr Comp Physiol 2002; 282 (1): R259-66
193. Buxton OM, Lee CW, L'Hermite-Baleriaux M, et al. Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase. Am J Physiol Regul Integr Comp Physiol 2003; 284 (3): R714-24
194. Atkinson G, Drust B, Reilly T, et al. The relevance of melatonin to sports medicine and science. Sports Med 2003; 33 (11): 809-31
195. Yamanaka Y, Hashimoto S, Tanahashi Y, et al. Physical exercise accelerates reentrainment of human sleep-wake cycle but not of plasma melatonin rhythm to 8-h phase-advanced sleep schedule. Am J Physiol Regul Integr Comp Physiol 2010; 298 (3): R681-91
196. Waterhouse J, Edwards B, Nevill A, et al. Do subjective symptoms predict our perception of jet-lag? Ergonomics 2000; 43 (10): 1514-27
197. Atkinson G, Davenne D. Relationships between sleep, physical activity and human health. Physiol Behav 2007; 90 (2-3): 229-35
198. Mistlberger RE, Skene DJ. Nonphotic entrainment in humans? J Biol Rhythms 2005; 20 (4): 339-52
199. Fuller PM, Lu J, Saper CB. Differential rescue of light- and food-entrainable circadian rhythms. Science 2008; 320 (5879): 1074-7
200. Saper CB, Fuller PM. Inducible clocks: living in an unpredictable world. Cold Spring Harb Symp Quant Biol 2007; 72: 543-50
201. Wu T, Ni Y, Kato H, et al. Feeding-induced rapid resetting of the hepatic circadian clock is associated with acute induction of Per2 and Dec1 transcription in rats. Chronobiol Int 2010; 27 (1): 1-18
202. Kohsaka A, Bass J. A sense of time: how molecular clocks organize metabolism. Trends in endocrinology and metabolism: TEM 2007; 18 (1): 4-11
203. Waterhouse J. Chronobiology and nutrition. In: MacLaren D, editor. Nutrition and sport. Philadelphia (PA): Churchill Livingstone, 2007: 207-28
204. Reilly T, Waterhouse J, Burke LM, et al. Nutrition for travel. J Sports Sci 2007; 25 Suppl. 1: S125-34
205. Hirao A, Tahara Y, Kimura I, et al. A balanced diet is necessary for proper entrainment signals of the mouse liver clock. PLoS One 2009; 4 (9): e6909
206. Mendoza J, Pevet P, Challet E. High-fat feeding alters the clock synchronization to light. J Physiol 2008; 586 (Pt 24): 5901-10
207. Oike H, Nagai K, Fukushima T, et al. High-salt diet advances molecular circadian rhythms in mouse peripheral tissues. Biochem Biophys Res Commun 2010; 402 (1): 7-13
208. Ehret CF, Scanlon LW. Overcoming jet lag. New York (NY): Berkley Books, 1983
209. Krauchi K, Cajochen C, Werth E, et al. Alteration of internal circadian phase relationships after morning versus evening carbohydrate-rich meals in humans. J Biol Rhythms 2002 Aug; 17 (4): 364-76
210. Laboratory UoCAN [online]. Available from URL: http://www.antijetlagdiet.com [Accessed 2011 Dec 5]
211. Hanauer SB. Jet lag: life in the fast (and feast) lane [editorial]. Nat Clin Pract Gastroenterol Hepatol 2008; 5 (7): 349
212. Reynolds Jr NC, Montgomery R. Using the Argonne diet in jet lag prevention: deployment of troops across nine time zones. Mil Med 2002; 167 (6): 451-3
213. Hirao A, Nagahama H, Tsuboi T, et al. Combination of starvation interval and food volume determines the phase of liver circadian rhythm in Per2: luc knock-in mice under two meals per day feeding. Am J Physiol Gastrointest Liver Physiol 2010; 299 (5): G1045-53
214. Bechtold DA. Energy-responsive timekeeping. J Genet 2008; 87 (5): 447-58
215. Eastman CI, Gazda CJ, Burgess HJ, et al. Advancing circadian rhythms before eastward flight: a strategy to prevent or reduce jet lag. Sleep 2005; 28 (1): 33-44

216. Stewart KT, Hayes BC, Eastman CI. Light treatment for NASA shiftworkers. Chronobiol Int 1995; 12 (2): 141-51
217. Morgan L, Hampton S, Gibbs M, et al. Circadian aspects of postprandial metabolism. Chronobiol Int 2003; 20 (5): 795-808
218. Harma MI, Ilmarinen J, Knauth P, et al. Physical training intervention in female shift workers: II. The effects of intervention on the circadian rhythms of alertness, short-term memory, and body temperature. Ergonomics 1988; 31 (1): 51-63
219. Costa G, Lievore F, Casaletti G, et al. Circadian characteristics influencing interindividual differences in tolerance and adjustment to shiftwork. Ergonomics 1989; 32 (4): 373-85
220. Waterhouse J, Edwards B, Nevill A, et al. Identifying some determinants of “jet lag” and its symptoms: a study of athletes and other travellers. Br J Sports Med 2002; 36 (1): 54-60

Correspondence: Dr *Sarah Forbes-Robertson*, Sport and Exercise Science Portfolio, School of Engineering, Swansea University, Swansea, SA2 8PP, UK.
E-mail: s.forbes-robertson@swansea.ac.uk or
sarah_forbes_robertson@hotmail.com